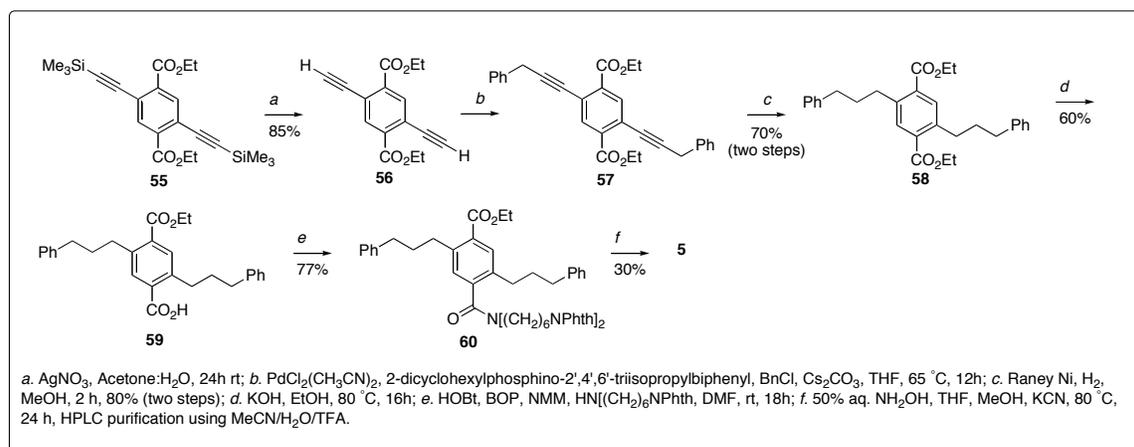


Figure S5

Synthesis of Analog 5



Diethyl 2,5-diethynylterephthalate (56): To a solution of **55** [1] (0.15 g, 0.361 mmol) in acetone (10 mL) was added a solution of AgNO_3 (0.03 g, 0.18 mmol) in H_2O (5 mL) and the reaction mixture was stirred in dark for 24 hours at room temperature[2]. The reaction mixture was poured on to a saturated brine solution (20 mL), filtered through Celite and washed with EtOAc. The layers were separated; the organic layer was dried over anhydrous MgSO_4 and concentrated *in vacuo*. MPLC purification of the residue using a gradient of Hex:EtOAc gave **51** as a white solid (0.08 mg, 85%). ^1H NMR (CDCl_3) δ 8.14 (s, 2H), 4.40 (q, $J = 7.2$ Hz, 4H), 3.51 (s, 2H) and 1.40 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (CDCl_3): δ 164.73, 136.80, 135.30, 122.74, 85.12, 81.03, 62.19 and 14.37.

Diethyl 2,5-bis(3-phenylprop-1-ynyl)terephthalate (57): A disposable vial equipped with a screw cap and a stir bar was charged with $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (2.40 mg, 0.0093 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (13.0 mg, 0.0273 mmol), and Cs_2CO_3 (0.17 g, 0.522 mmol). The vial was evacuated and back-filled with nitrogen three times. A solution of benzyl chloride (0.086 g, 0.680 mmol) and **51** (0.061 g, 0.226 mmol) in anhydrous THF (8 mL) was then added and the solution was stirred at 65 °C for 12 hours[3]. After cooling to room temperature, the reaction mixture was filtered over Celite and concentrated *in vacuo*.

The benzyl alkyne was found to be unstable during column chromatography, hence the crude reaction mixture was subjected to hydrogenation with Raney-Ni without any purification.

Diethyl 2,5-bis(3-phenylpropyl)terephthalate (58): A solution of crude product **57** from the above reaction in MeOH (10 mL) was added Raney Nickel (200 μ L, slurry in water) and the reaction mixture was stirred at room temperature for 2 hours under a balloon of hydrogen. The reaction mixture was filtered through Celite and concentrated *in vacuo*. MPLC purification of the residue using a gradient of Hex:EtOAc gave **53** as a colorless oil (0.72 mg, 70% yield for two steps). ^1H NMR (CDCl_3) δ 7.68 (s, 2H), 7.30-7.25 (m, 4H), 7.22-7.16 (m, 6H), 4.34 (q, $J = 7.2$ Hz, 4H), 2.96 (t, $J = 7.6$ Hz, 4H), 2.69 (t, $J = 8.0$ Hz, 4H), 1.99-1.89 (m, 4H) and 1.38 (t, $J = 6.8$ Hz, 6H). ^{13}C NMR (CDCl_3): δ 167.62, 142.40, 141.15, 133.01, 128.67, 128.52, 125.98, 61.40, 36.09, 33.79, 33.45 and 14.53.

4-(Ethoxycarbonyl)-2,5-bis(3-phenylpropyl)benzoic acid (59): To a solution of **58** (0.05 gm, 0.109 mmol) in EtOH (10 mL) was added KOH (0.012 g, 0.218 mmol) and the reaction mixture was stirred at 80 $^\circ\text{C}$ for 16 hours. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in water (10 mL), neutralized with 1 N HCl and extracted with EtOAc (3 x 10 mL). The combine organic extracts were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. MPLC purification of the residue using a gradient of Hex:EtOAc gave **59** as a white solid (28 mg, 60%) with little impurities of the diacid. This product was carried forward to next step without any further purification.

Ethyl 4-bis(6-(1,3-dioxisoindolin-2-yl)hexyl)carbamoyl)-2,5-bis(3-phenylpropyl)benzoate (60): A solution of **59** (0.025 g, 0.058 mmol), **14x** (0.036 g, 0.076 mmol), BOP (0.014 mg, 0.103 mmol), HOBT (0.047 g, 0.106 mmol) and NMM (13 μ L, 0.119 mmol) in anhydrous DMF (5 mL) was stirred at room temperature for 16 hours. The reaction mixture was

partitioned between water (10 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The organic layers were dried over MgSO₄, filtered and then concentrated *in vacuo*. MPLC purification of the residue using a gradient of Hex:EtOAc gave **50** as a pale yellow oil (0.04 g, 77%). ¹H NMR (CDCl₃) δ 7.84-7.81 (m, 4H), 7.71-7.69 (m, 4H), 7.26-7.22 (m, 5H), 7.17-7.13 (m, 6H), 6.99 (s, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.66-3.59 (m, 2H), 3.54 (t, *J* = 7.2 Hz, 2H), 3.24-3.17 (m, 2H), 2.93 (q, *J* = 7.6 Hz, 4H), 2.63 (q, *J* = 7.6 Hz, 4H), 2.60-2.53 (m, 2H), 2.02-1.91 (m, 2H), 1.91-1.85 (m, 4H), 1.73-1.69 (m, 2H), 1.64-1.54 (m, 2H), 1.54-1.47 (m, 2H) and 1.47-1.35 (m, 9H).

N',N'-Bis(6-aminohexyl)-N⁴-hydroxy-2,5-bis(3-phenylpropyl)terephthalamide (5): To a stirred solution of **50** (0.038 g, 0.043 mmol) in MeOH:THF (1:1, 8 mL) was added 50 % aqueous hydroxylamine (1 mL) followed by catalytic amount of KCN . The resulting mixture was stirred at 80 °C for 24 hours. After the solvent was removed *in vacuo*, the residue was subjected to HPLC purification, which gave **5•2TFA** as a colorless oil (11 mg, 30%). The semi – preparative and analytical HPLC retention time for **5•2TFA** are 15.41 (eluting time: 30 minutes) and 12.9 minutes (eluting time: 20 minutes) respectively. ¹H NMR (CD₃OD) δ 7.81 (s, 1H), 7.28-7.23 (m, 4H), 7.20-7.12 (m, 6H), 7.05 (s, 1H), 3.67-3.62 (m, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 3.12-2.92 (m, 4H), 2.68-2.52 (m, 6H), 2.04-1.92 (m, 2H), 1.92-1.82 (m, 2H), 1.72-1.62 (m, 4H), 1.54-1.34 (m, 8H) and 1.12-1.02 (m, 4H).

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